

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of )  
)  
Felix KRATZ ) Group Art Unit: Unassigned  
)  
Continuation of Application No.: 09/254,598, ) Examiner: Unassigned  
filed March 11, 1999 )  
)  
Filed: August 20, 2001 )  
)  
For: ANTINEOPLASTIC CONJUGATES )  
OF TRANSFERRIN, ALBUMIN )  
AND POLYETHYLENE GLYCOL )

**PRELIMINARY AMENDMENT**

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

Prior to examination on the merits, please amend the above-identified application as follows:

**IN THE CLAIMS:**

Please cancel claims 1-6 without prejudice or disclaimer.

Please add new claims 7-14 as follows.

7. (New) A conjugate of a cytostatic compound and transferrin or albumin or a polyethylene glycol, wherein:

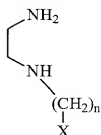
- (a) said cytostatic compound is coupled via a spacer comprising a group which is derived from a maleinimido group, to thiolated transferrin or thiolated albumin or to polyethylene glycol having at least one HS or H<sub>2</sub>N group; or
- (b) 2 to 30 equivalents of said cytostatic compound are each coupled via a spacer comprising a group which is derived from a maleinimido group, to thiolated albumin, wherein the thiolated albumin is conjugated via a group which is derived from a bismaleinimido compound to transferrin or a monoclonal antibody which is directed to a tumor associated antigen; and

wherein said thiolated transferrin or said thiolated albumin has 1 to 30 HS groups on the average, and said polyethylene glycol has a mass of about between 5,000 and 200,000 Da.

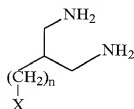
8. (New) The conjugate according to claim 7, wherein said cytostatic compound is selected from the group consisting of anthracyclines, nitrogen mustard gas derivatives, purine or pyrimidine antagonists, folic acid antagonists, taxoids, camptothecines, podophyllotoxin derivatives, vinca alkaloids and *cis*-configured platinum(II)-complexes.

9. (New) The conjugate according to claim 7, wherein said cytostatic compound is selected from the group consisting of doxorubicine, daunorubicine, epirubicine, idarubicine, mitoxandrone, chloroambucil, melphalan, 5-fluorouracil, 5'-deoxy-5-fluorouridine, thioguanine, methotrexate, paclitaxel, docetaxel, topotecane, 9-aminocamptothecine, etoposide, teniposide, mitopodozide, vinblastine, vincristine, vindesine, vinorelbine and compounds of the general formulas I, II, III or IV:

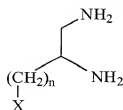
Formula I



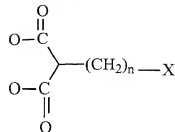
Formula II



Formula III



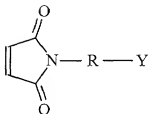
Formula IV



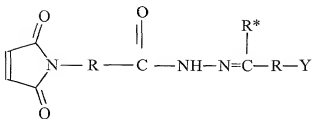
wherein  $n = 0-6$ ,  $X = -\text{NH}_2$ ,  $-\text{OH}$ ,  $-\text{COOH}$ ,  $-\text{O}-\text{CO}-\text{R}-\text{COR}^*$  or  $-\text{NH}-\text{CO}-\text{R}-\text{COR}^*$ ,  
 wherein  $\text{R}$  is an aliphatic carbon chain having 1-6 carbon atoms or is a substituted or  
 unsubstituted phenylene group and  $\text{R}^*$  is  $\text{H}$ , phenyl or alkyl having 1-6 carbon atoms.

10. (New) The conjugate according to claim 7, wherein said cytostatic compound  
 having said spacer comprising a group which is derived from a maleinimido group, is  
 formed through reaction of said cytostatic compound with a maleinimide compound of the  
 formula V, VI or VII:

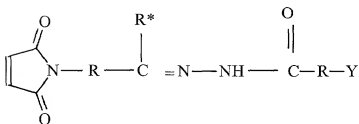
Formula V



Formula VI



Formula VII



wherein, R is an aliphatic carbon chain having 1-6 carbon atoms or a substituted or unsubstituted benzyl group or a substituted or unsubstituted phenylene group, Y = -OH, -COOH, -COCl, -CONH-(CH<sub>2</sub>)<sub>n</sub>-OH, -COO-(CH<sub>2</sub>)<sub>n</sub>-NH<sub>2</sub>, -COO-(CH<sub>2</sub>)<sub>n</sub>-NHNH<sub>2</sub>, -SO<sub>3</sub>H, -

SO<sub>3</sub>Cl, -SO<sub>2</sub>-NHNH<sub>2</sub>, -O-COCl, -CHO or -COR\*, wherein n = 1-6 and R\* represents H, phenyl or alkyl having 1-6 carbon atoms, and the thus obtained maleinimide derivative of said cytostatic compound is coupled to said thiolated albumin or said thiolated transferrin or said polyethylene glycol, wherein the chemical linkage between said cytostatic compound and said maleinimide compound occurs through an amide, ester, imine, hydrazone, carboxyl hydrazone, oxycarbonyl, acetal or ketal bond.

11. (New) A method for the production of a conjugate of a cytostatic compound and transferrin or albumin or a polyethylene glycol according to claim 7, comprising the steps of:

- (a) reacting a cytostatic compound with a maleinimide compound, such that maleinimide derivatives of said cytostatic compound are produced, wherein the chemical linkage between said cytostatic compound and said maleinimide compound occurs through an amide, ester, imine, hydrazone, carboxyl hydrazone, oxycarbonyl, acetal or ketal bond; and
- (b) (i) coupling said maleinimide derivative obtained in step (a) of the cytostatic compound to thiolated transferrin or albumin having 1 to 30 HS groups on the average or to polyethylene glycol having at least one HS or H<sub>2</sub>N group and having a mass of about between 5,000 and 200,000 Da; or

- (ii) loading thiolated albumin with 2 to 30 equivalents of said maleinimide derivatives obtained in step (a) of the cytostatic compound and conjugating with transferrin or a monoclonal antibody directed to a tumor-associated antigen via a group which is derived from a bismaleinimido compound.

12. (New) A pharmaceutical composition, comprising the conjugate according to claim 7, optionally together with carriers and auxiliary agents.

13. (New) Method for the treatment of a cancer disease, comprising the step of treating an organism having a cancer disease with the conjugate of claim 7.

14. (New) Method according to claim 13, wherein said cancer disease comprises bladder, lung, mamma, melanoma or prostate carcinomas.

**REMARKS**

Entry of the foregoing prior to examination on the merits and in light of the remarks which follow are respectfully requested.

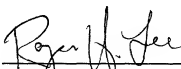
By the above amendments, claims 1-6 have been canceled. New claims 7-14 are directed to further aspects of the present invention. Support for new claims 7-14 can be found in the specification at least at pages 40-50.

If there are any questions concerning this paper or the application in general, the Examiner is invited to telephone the undersigned.

Respectfully submitted,

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